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MER/29

Triparanol (MER/29 - Merrell) is a new drug promoted as the first safe agent to inhibit body-produced cholesterol. It is offered for use in hypercholesterolemia, coronary artery disease and generalized atherosclerosis. MER/29 is structurally similar to chlorotrianisene, a synthetic estrogen, but it has the unique property of partially blocking the synthesis of cholesterol from its precursor sterol, 24-dehydrocholesterol (desmosterol). Though there is no clear evidence that MER/29 can reverse the deposition of cholesterol or other lipids in atherosclerotic arteries in man, the drug can reduce hypercholesterolemia in many patients.

It has never been established, however, that reduction of blood cholesterol levels prevents coronary artery disease or generalized atherosclerosis, or that it improves the prognosis in these disorders. Nevertheless, the well-established association between abnormal lipid metabolism and clinical atherosclerosis has convinced many physicians of the desirability of reducing blood cholesterol levels in patients with hypercholesterolemia, with clinical signs or symptoms of atherosclerotic disease, or with a bad family history of coronary disease.

METHODS OF REDUCTION - Various means of reducing blood cholesterol levels have been used. Dietary measures have included both fat-free diets, and diets in which unsaturated fats (such as corn oil) make up about 75 per cent of the total fat intake. These measures are effective but difficult to follow. A variety of drugs have been used, including estrogenic hormones, thyroid or thyroxine analogues, nicotinic acid, beta-sitosterols, and a number of different combinations of concentrates of unsaturated fatty acids in oils. While these drugs are often effective, side effects, sometimes severe, are common.

How MER/29 will fit into this picture is still to be determined. The drug was introduced some months ago after considerable experimental work in animals and limited short-term clinical tests. Most of the published reports on the drug appear in the Proceedings of the Conference on MER/29 (Progress in Cardiovascular Dis., 2:485, May 1960). (For a follow-up report on the experience of one group of participants in the conference see W. Hollander, et al., JAMA, 174:5, Sept. 3, 1960.) These reports indicate that the drug reduces blood cholesterol anywhere from 10 to 55 per cent in at least half of patients, with a mean reduction of about 25 per cent. Although improvement has been reported in some patients with insufficiency of the coronary and peripheral arteries who received MER/29, the only controlled trial (H. I. Russek, Progress in Cardiovascular Dis., 2:578, 1960)

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produced no evidence of clinical improvement attributable to the drug in a series of 40 patients with angina.

An important question about the drug arises from the fact that 24-dehydrocholesterol, the precursor of cholesterol, accumulates in patients under treatment with MER/29 (D. Steinberg, et al., ibid., p. 586). Dr. Steinberg and his associates ask: "What are the long-term biological effects of 24-dehydrocholesterol and to what extent is it atherogenic?" Until such questions are answered, claims for the safety of the drug cannot be fully accepted.

CHANGES IN LEVELS - Another question, which applies to all methods of treatment of hypercholesterolemia, arises from the unreliability of cholesterol determinations as guides to effectiveness of a treatment program. Relatively few laboratories are able to determine cholesterol levels accurately. Furthermore, blood cholesterol fluctuates in patients with coronary artery disease (as well as in normal persons), and the fluctuations are wide and unpredictable. They are affected not only by diet, but also by emotional stress and physical activity. Weight reduction alone can depress the blood cholesterol, regardless of the cause of the elevation. Factors such as these indicate the need for controlled trials of cholesterol-reducing drugs, and make valid judgments difficult in the absence of such trials.

Immediate or short-term toxic and side effects with MER/29 were few and slight in the various reported studies. Nausea was uncommon except with large doses, but occasional skin rashes occurred. Although no clear-cut evidence of liver damage was shown, three of 28 patients showed an increase in bromosulfophthalein (BSP) retention and a slight increase in alkaline phosphatase (W. Hollander, et al., ibid., p. 637). Some female patients showed cytological estrogenic effects of the drug, and in one elderly patient slight vaginal bleeding occurred for one day. R. G. Gould (ibid., p. 492) suggested that tolerance to the drug might become a problem.

DOSAGE - The recommended dose of the drug is one 250-mg. capsule daily. When reduction of blood cholesterol does occur, it usually begins about two of three weeks after therapy is started. When the drug is discontinued, there is usually an elevation of cholesterol to previous levels.

To summarize, MER/29 is unique among blood cholesterol reducing agents in its mechanism of action. Short-term studies indicate that it is a relatively non-toxic agent, capable of reducing blood cholesterol in many patients. There is no proof, however, that the drug influences the pathologic basis or the clinical course of atherosclerosis of the coronary or other arteries, or that it is superior to other cholesterol-reducing agents or diets in its effects on blood cholesterol. Because MER/29 causes an accumulation of 24-dehydrocholesterol in the body and because the metabolic effects of this sterol are not known, Medical Letter consultants believe that the drug should still be reserved for experimental trial. If continued studies show that it is both safe and effective over prolonged periods, its convenience will give it an important advantage over dietary methods for many patients. At present the safest method of reduction of blood cholesterol is the use of unsaturated fats for at least three quarters of the total

fat intake. But - to repeat - it has not been shown that the reduction of blood cholesterol levels serves any therapeutic purpose. (The cost of MER/29 is about 35¢ per 250 mg. capsule.)

ELIPTEN

Aminoglutethimide (Elipten - Ciba) is a glutarimide derivative claimed to have greater anticonvulsant effect with less sedative effect than its analogue, glutethimide (Doriden). It is offered for use alone or as an adjunct to other drugs for improved control in "most types" of epilepsy. The manufacturer states that the average adult dose is 250 mg. three times a day, but most patients require much larger doses.

The most enthusiastic report on this drug (C. H. Carter, Dis. Nerv. Syst., 21:50, 1960) lacks sufficient data to allow evaluation. W. Fabisch (J. Mental Sci., 105:448, 1959) concludes from his study that Elipten is moderately effective in doses of 1000 mg. or more per day; in many of the patients the drug had to be stopped because of side reactions. Others (G. D. LaVeck, Dis. Nerv. Syst., 21:230, 1960; G. D. Niswander and I. Karacan, Am. J. Psychiatry, 116:260, 1959) find the drug useful in a minority of patients, with excessive drowsiness, nausea, ataxia and choreiform movements on the large doses often required. In several studies there was an appreciable incidence of skin eruptions even on modest doses.

There can be no objection to a trial of Elipten in patients refractory to the older anticonvulsants, but the available data do not indicate that it is as reliable as older, time-tested preparations (such as the hydantoins, barbiturates, oxazolidinediones and succinamides); there is no clear evidence that its use along with other drugs improves control of patients refractory to the older agents. (See The Medical Letter, 1:97, 1959, for a review of anti-epilepsy drugs.)

ACNE CLEANSERS

The action of the sex hormones on the pilosebaceous apparatus is probably a major factor in the development of acne, but no safe or consistently effective therapeutic measures are available to control the action of the hormones. On the other hand, follicular plugging (comedo) is always the precursor of the acne lesion, and plugging is amenable to topical therapy.

An important part of topical therapy is the use of cleansers. A number of proprietary preparations, most of them containing synthetic detergents, abrasives or other agents in place of or in addition to soap, are offered for the treatment of acne. While they may be no more effective than ordinary soap in removing dirt, surface oils, sweat and debris, those containing synthetic detergents or abrasives are likely to be more effective than ordinary soaps in producing the peeling required to relieve follicular plugging.

OTHER AGENTS - Keratolytic agents such as sulfur and salicylic acid are

found in some preparations along with detergents, wetting agents and abrasives, but it is difficult to understand how keratolytic agents can be effective in such brief contact with the skin. They do not remain on the skin after the cleansing operation has been completed.

Certain topical antibacterial agents (hexachlorophene, bithionol, and trichloro-carbanilide) which are now being added to some cleansers do, however, remain on the skin. Residues of these materials, which have very low solubility in water, are deposited on the skin and are not rinsed off during the washing procedure. It has never been definitely determined whether bacteria play an important role in the pathogenesis of acne lesions, nor whether the residual antiseptics are effective in acne. Nevertheless, there appears to be no objection to trying to reduce the resident flora on the skin of a patient with a tendency to acne, and the residual antiseptics will accomplish such reduction.

SPECIAL CLEANSERS - Lengthy massage and scrubbing with any regular toilet soap will be helpful in mild acne. In more severe cases one of the preparations in the following list may be helpful. The last two of the preparations are likely to have the greatest peeling effect.

1. Acne Aid Detergent Soap (Steifel), containing 10.5% sulfated vegetable oil and 89.5% neutral soap.
2. pHisoderm (Winthrop), a synthetic detergent containing sodium-p-terocytylphenoxy-ethoxyethoxy ethyl ether sulfonate; pHisohex is the same as pHisoderm with 3% hexachlorophene.
3. Acne Dome Cleanser (Dome), a soapless skin cleanser containing 2% sulfur, 2% salicylic acid, 1% bithionol and colloidal soy bean fraction.
4. Fostex Cake and Fostex Cream (Westwood), containing a combination of cleansing and wetting agents (sodium lauryl sulfoacetate, sodium alkyl polyether sulfonate, sodium dioctyl sulfosuccinate), 2% sulfur, 2% salicylic acid, and 1% hexachlorophene.
5. Cosmasul (Cosmata), a cream soap containing sulfur and an abrasive (calcium carbonate granules).
6. Brasivol (Steifel), a cream consisting of soap and synthetic detergent with an abrasive (fused synthetic aluminum oxide) and 1% hexachlorophene. This product is available in three grades: fine, medium, and rough.

The directions accompanying these products generally call for massaging, scrubbing, or lathering for periods up to five minutes. Depending on the product, varying degrees of superficial irritation are produced, resulting in redness, dryness and desquamation of the skin. Especially when used with a topical lotion such as Lotio Alba NF (freshly prepared), they will often go a long way in benefiting the patient's skin and psyche. Small maintenance doses (about 250 mg. daily) of such oral antibiotics as the tetracyclines, erythromycin and triacetyloleandomycin may be worth trying in severe cases to help combat suppuration.

CORRECTION - HUMATIN (The Medical Letter, 2:53, July 8, 1960). The statement, "Animal experiments have shown ... that parenteral administration can cause severe liver damage," should have said kidney, not liver damage. As pointed out, toxicity is very low when the drug is given orally.

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